DETAILED ACTION

1. Applicant's remarks filed October 29, 2009 are acknowledged. Claims 23-44 are pending. Claims 23-31 and 41-44 are withdrawn from consideration being drawn to non-elected subject matter. Claims 32-40 are under examination.

Specification

2. The objection to the specification for lack of sequence identifiers is withdrawn in view of Applicant's amendment. Likewise, the objection to the drawings (*i.e.*, Figure 1) is withdrawn.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-36, 38 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim *et al.* (*Cancer Research*, December 15, 2002, 62:7234-7240, "Kim"). Kim discloses the administration of E7 protein (full length, 98 amino acids) and CpG-oligodeoxynucleotide (CpG-ODN, an adjuvant that naturally activates dendritic cells) to mice and subsequent protective immunity against challenge with HPV-16 (E6/E7) immortalized tumor cells (abstract). The sequence of the protein is expected to be at least 80% identical to 46 amino acids of SEQ ID NO: 1 (HPV-16 E7 protein) because Kim's E7 protein was not mutated. Although Kim did not synthetically produce the protein, it is expected to have the same properties and at least 80% identity to SEQ ID NO: 1. The E7 protein was stabilized in buffers (pharmaceutically acceptable

carrier) and administered as a vaccine (pre-challenge). Although Kim does not note the absence of nucleic acid encoding E7, none is expected to be present in Kim's composition because Kim purifies the protein.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that it is expected that Kim's composition comprising the E7 protein contains contaminating nucleic acids because it was produced recombinantly. Applicant argues that the instantly claimed composition does not contain contaminating nucleic acids because it is produced synthetically. Applicant notes that the claim requires the absence of nucleic acid.
  - In response to Applicant's argument, the Office notes that claim 32 requires the absence of nucleic acid *encoding the amino acid sequence* (*i.e.*, E7, for example) which does not mean that there cannot be any other nucleic acids present in the composition. Thus, even if there were contaminating nucleic acids in Kim's composition, as long as they do not encode E7, they are permissible according to the claim language. As noted in the rejection above, Kim's composition is purified, so the presence of contaminating nucleic acids is not expected even *if* the claims recited the embodiment of being entirely free from any nucleic acid.
- Applicant notes that Kim's protein is 23 kDa and includes a His tag. Applicant argues that the size of the protein and the presence of the His tag render the prior art's protein distinct from Applicant's protein. Applicant asserts that their protein is structurally different from the recombinantly produced protein.

- In response to Applicant's argument, the term "synthetic" does not impart any meaning to the protein in terms of its content. A protein of any size and comprising a His tag can be synthetically produced if desired. It appears that Applicant assigns structural distinction to the term "synthetic". However, the Office does not agree with this interpretation. If Applicant wants to exclude the presence of a His tag, or limit the size of the protein, then the claim limitations must clearly set forth such embodiments as opposed to relying on the term "synthetic" to limit the content of the protein. (From another perspective, note that just because a protein is recombinantly produced, does not mean that is necessarily has a His tag or a larger molecular weight.) Therefore, the rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kim as applied to claim 32 above, and further in view of Zwaveling *et al.* (*The Journal of Immunology*, 2002, 269:350-358, "Zwaveling") and Turner *et al.* (*The Journal of Immunology*, 2001, 166:89-94, "Turner"). Claim 39 is directed to a composition comprising an antigen that comprises an amino acid sequence that is at least 80% identical to 46 contiguous amino acids of a naturally occurring antigen of a pathogen, and additionally comprises anti-CD40 antibodies. The teachings of Kim

are summarized above. Kim does not teach or suggest the use of anti-CD40 antibodies in combination with the HPV-16 E7 protein/CpG-ODN construct.

However, it would have been obvious to include an agent that activates dendritic cells, such as anti-CD40 antibodies. One would have been motivated to activate the DCs in order to achieve a greater immune response. Zwaveling teaches that anti-CD40 antibodies are DC-activating agents. Given that Kim uses the CpG-ODN for activating DCs, one would have had a reasonable expectation of success that the inclusion of another DC-activating agent, such as anti-CD40 antibodies, would have resulted in the activation of more DCs than the CpG/ODN construct alone. Further, Turner teaches that anti-CD40 antibodies induce antitumor and antimetastic effects in tumor-bearing mice (abstract). Given the positive effects of anti-CD40 antibodies, one would have also been motivated to include the antibodies in a treatment composition/regimen as part of a multi-faceted approach. Therefore, the claimed embodiment would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been addressed above.

5. (*New Rejection*) Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kim as applied to claims 32-34 above, and further in view of Carson *et al.* (WO 98/16247, "Carson"). The claim is drawn to an embodiment wherein the protein is covalently conjugated to an adjuvant. Kim suggests the use of CpG-ODN in conjunction with E7 protein as an adjuvant, but the specific suggestion to conjugate the two molecules together is absent. However, it would have been obvious to covalently conjugate the CpG-ODN with the E7 protein in order to enhance the adjuvant effect of the CpG-ODN. One would have been motivated by Carson's

teaching that immunostimulatory polynucleotide-immunomodulatory molecules (such as CpG sequences) conjugated to protein antigens result in a very effective immune response compared to unconjugated delivery of antigen and adjuvant (see abstract, page 10 first paragraph, page 14, last paragraph, and page 17, first full, paragraph). One would have had a reasonable expectation of success that the conjugation of the adjuvant with the protein would have yielded an improved immune response given that Carson's teachings are to be broadly applied to a variety of immunostimulatory sequences and protein antigens. Therefore, the claimed embodiment would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

6. No claim is allowed. This action is non-final in view of the new grounds of rejection, specifically the rejection of claim 37. Any inconvenience is regretted.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648